Regioselective Photoredox Catalyzed Cycloadditions of Acyclic Carbonyl Ylides

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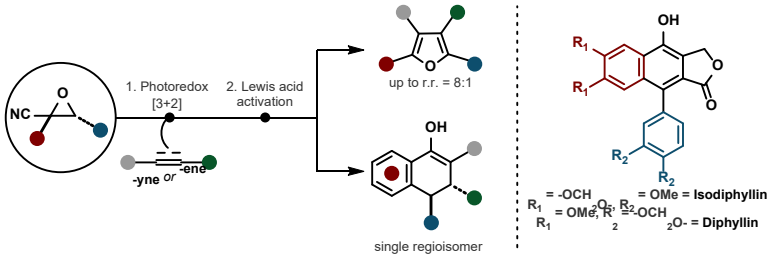
Supporting Information Placeholder

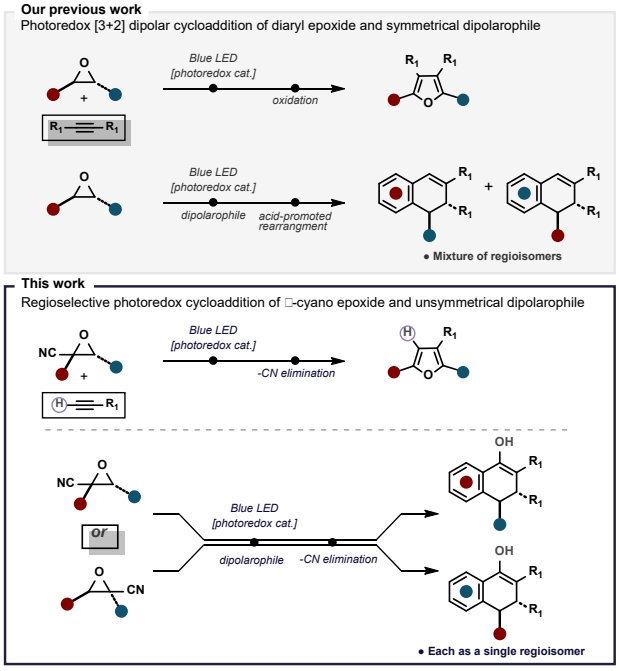


ABSTRACT: A photoredox catalyzed [3+2] dipolar cycloaddition between acyclic carbonyl ylides generated from α-cyano epoxides and dipolarophiles is described. This method, influenced by anionic charge localization and temperature control, enabled the synthesis of regioselective functionalized cyclic ethers. By leveraging different dipolarophiles, Lewis acid mediated activation afforded either furan or hydroxy-dihydronaphthalene scaffolds. A direct synthesis of lignan natural products isodiphyllin and diphyllin is achieved by exploiting the nitrile's reactivity as a directing handle for the desired regioisomer.

Selective [3+2] dipolar cycloaddition of acyclic carbonyl ylides with dipolarophiles is a highly useful approach to synthesize five membered oxygen heterocycles with complex saturation and substituent variation.[1] Such cyclic ethers (tetrahydro-, dihydro-, and furan) are an important structural motif found in numerous bioactive natural products and pharmaceuticals.[2] Unfortunately, while [3+2] cycloadditions remain a viable approach to the aforementioned products, 1,3-dipolar carbonyl ylides have been underutilized amongst the chemical community due to either expensive catalysts or the inability to generate ylide intermediates effectively under mild conditions.[3] To address these shortcomings, our group has developed an organo-photoredox protocol to generate carbonyl ylides from diaryl epoxides, which produces cyclic ethers upon cyclization with dipolarophiles. These cyclic ethers were then used enroute to classical lignan natural product total syntheses (**Scheme 1**).[4] While our methods were broad in scope and effectively provided a unified approach to this lignan natural product subclass, achieving regioselectivity during cycloaddition through this method was unrealized.

The synthesis of aryl- and dihydro-naphthalene lignan derivatives, with diverse functional group reactivities, would be a powerful solution to optimizing biological activity and chemical/metabolic stability of this important class of natural products.[4b] However, unsymmetrical reaction partners in our

Scheme 1. Previous work on photoredox catalyzed [3+2] dipolar cycloadditions of carbonyl ylides and proposed strategy to improve the regioselectivity



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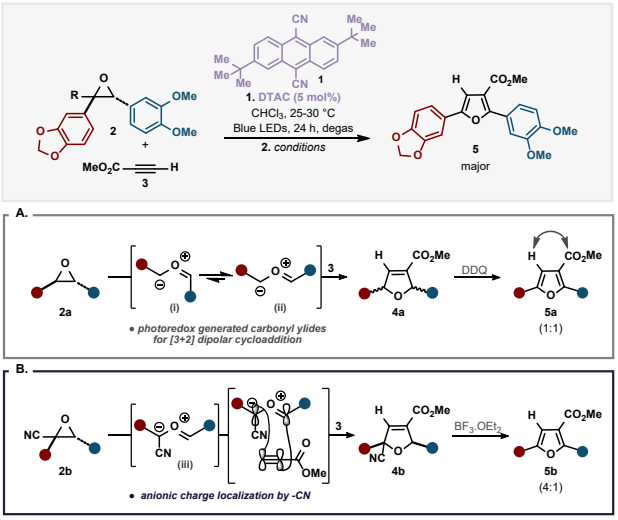
key cycloaddition were largely unexplored due to the inability to control regioselectivity. To address these limitations, we investigated a directing group which could (1) localize anionic charge on the ylide intermediate and (2) act as a handle for downstream reactions.

Historically, cycloadditions of cyclic 1,3-dipolar carbonyl ylide intermediates have enabled complex transformations enroute to natural products bearing oxy-cyclic backbones.[1a] The most notable reaction generates cyclic carbonyl ylides through rhodium catalysis of α-diazo ketones with an adjacent carbonyl group which participates in intramolecular cyclizations.[5] In contrast, acyclic carbonyl ylides commonly generated from epoxides *via* thermal, photochemical, and recently, chiral Lewis acid catalyzed means, participate in intermolecular cycloadditions with unsaturated C-C dipolarophiles.[6] Additionally, efforts to achieve regioselective reactions from acyclic carbonyl ylides have previously used epoxides bearing substituted aryl groups (*p*-CN or *p*-OMe) or α-electron-withdrawing groups (EWG), to localize the anionic charge of the ylide.[7] Inspired by these findings, we sought to gain regioselectivity using α-cyano diaryl epoxides under our photoredox process. We hypothesized that the cyano group would localize the anionic charge adjacent to the α-EWG (HOMO), thereby promoting regioselective addition to the unsymmetrical dipolarophile (LUMO).

Herein, we examine the factors influencing selectivity of photoredox generated carbonyl ylides using previously unexplored unsymmetrical epoxides (**Scheme 1**). We further investigate the regioselectivity achieved using these epoxides by analyzing the resulting cycloaddition products. Moreover, installation of the nitrile group successfully served as a directing handle in downstream reactions which enabled the total synthesis of lignan natural products isodiphyllin and diphyllin in 5 steps and unnatural derivatives as single products.

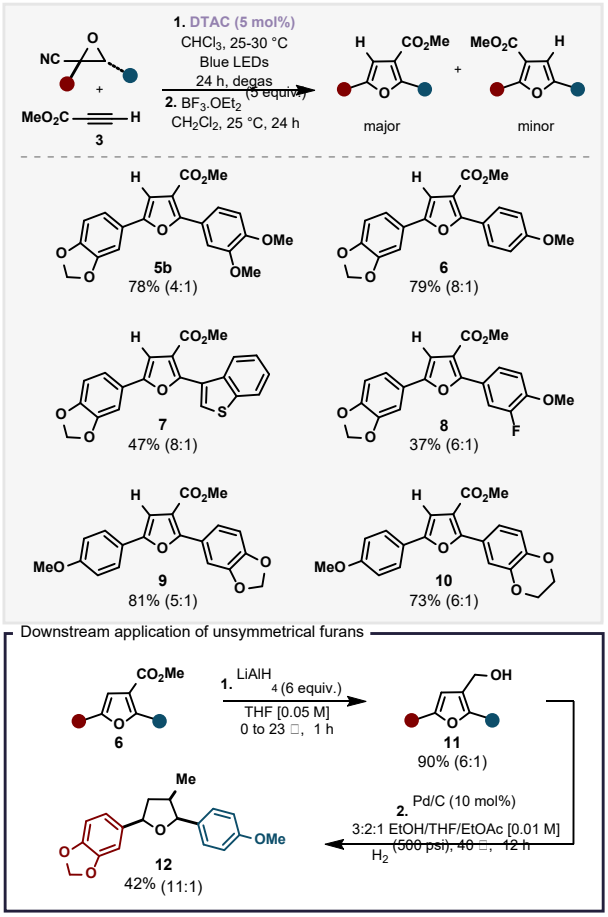
Scheme 2. Initial regioselective study of unsubstituted *vs* α-cyano substituted diaryl epoxides



We began the investigation by synthesizing epoxide **2a** *via* a one-pot Johnson-Corey-Chaykovsky reaction, and α-cyano-substituted epoxide **2b** through a Darzens condensation.[8] These epoxides were then evaluated in cycloaddition reactions using photoredox catalysts 2,6-ditert- butylanthracene-9,10-dicarbonitrile (DTAC, **1**) (λmax = 431 nm, [DTAC*/DTAC•−] = +1.81 V vs SCE) under blue LED irradiation with unsymmetrical dipolarophile **3** (**Scheme 2**).[4b] Epoxide **2a** afforded an equal mixture of regioisomers, **5a** (rr = 1:1), upon oxidation with DDQ. In contrast, starting with epoxide **2b**, the presence of the cyano group notably influenced regioselectivity providing **5b** (rr = 4:1), after Lewis acid-mediated cyanide elimination and subsequent aromatization.

With a focus on the photoredox generated carbonyl ylides from both **2a** and **2b**, we were interested in understanding the energy difference in the most stable conformer that produced the major product in the reaction sequence. There are four possible products with dipolarophile **3** using α-cyano epoxide **2b**, the major product **4b** is expected to arise from the more stable carbonyl ylide conformer (**iii**) wherein trapping with dipolarophile **3** should result in the cyano group being opposite to the methyl ester. DFT calculations show that the cyano-substituted carbonyl ylide (**iii**) from **2b** is in fact 3.2 kcal/mol more stable than for carbonyl ylide (**ii**) from **2a** (*Supporting Information*).[9] These calculations support our hypothesis that the acyclic α-cyano carbonyl ylide does indeed induce selectivity over diaryl unsubstituted epoxides under photoredox catalysis.

Scheme 3. Scope of unsymmetrical furans from α-cyano epoxides and methyl propiolate



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Next, we systematically screened the cycloaddition reaction conditions and evaluated the regioselectivity over 2 steps. Assessment of solvent and temperature revealed that chloroform provided the highest yield and regioselectivity. Remarkably, an optimal regioselectivity ratio of **6** (16:1) was achieved at -40 °C, albeit with a low yield (43%) (*Supporting Information*). This observation underscores the role of α-cyano epoxides in augmenting the regioselectivity of photoredox-catalyzed dipolar cycloadditions involving carbonyl ylides. Additionally, temperature control was found to further enhance the regioselectivity of the reaction.

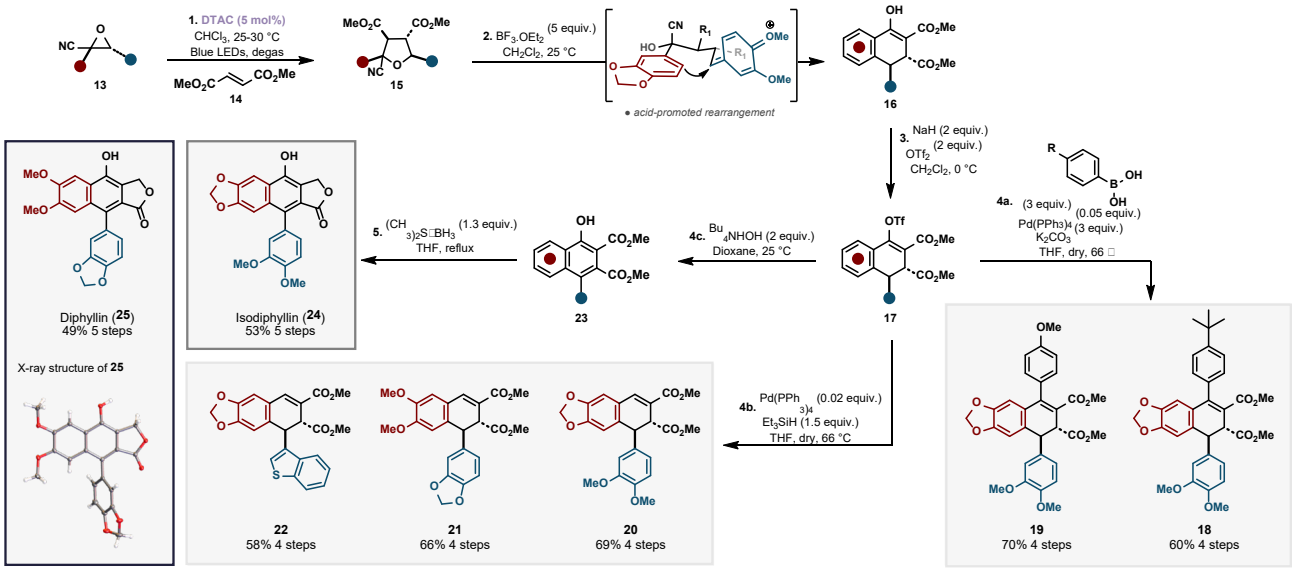
With the optimized conditions in hand, we investigated the substrate scope in **Scheme 3** using various α-cyano epoxides in the reaction. To streamline the efficiency of these reactions bearing different substituents, chloroform at room temperature was used to prioritize higher yields for a range of compounds. Polyoxygenated furan scaffolds (**5b**, **6**, and **9**) bearing methoxy groups at both the *para*- and *meta*- positions were obtained in high yields with moderate to good regioselectivity. Their electron and oxygen rich environments mimic many biologically active lignan natural product derivatives. Heterocyclic derivatives (**7** and **10**) 1,3-dioxolane, benzothiophene and 1,4-dioxolane were also obtained in good yields and with good regioselectivity and represent diverse building blocks for unnatural derivatives. Fluorinated substitution, known to stabilize lignans *in vivo*, was displayed and tolerated in the reaction as compound **8** albeit in low yield.[10] Unfortunately, these conditions failed to activate aryl groups lacking strong electron-donating substitutions. Moreover, benzyloxy substituents were not tolerated as they were easily cleaved by BF_3•OEt_2 in the reaction.

To demonstrate the applicability of these furan building blocks, we pursued the synthesis of talaumidin analogue **12** (**Scheme 3**).[11] Using furan **6**, $LiAlH_4$ reduction to alcohol **11** enabled direct hydrogenated with Pd/C to yield **12** (42%) with good regioselectivity (r.r. = 11:1). These results highlight the potential of unsymmetrical epoxides as carbonyl ylide precursors under photoredox catalysis, paving the way for their application in synthesis and medicinal chemistry.

We then explored the versatility of the nitrile group as a handle for downstream regioselective control enroute to lignan natural products. To start, α-cyano epoxide **13** (**Scheme 4**) was subjected to the previous photoredox conditions and engaged in a [3+2] dipolar cycloaddition with dipolarophile dimethyl fumarate (DMF) **14** to afford the resulting cyano-substituted tetrahydrofuran **15**. Subsequent incubation with BF_3•OEt_2 led to formation of the dihydronaphthol derivative through an intramolecular Friedel-Crafts arylation and successive cyanide elimination.[4b] As expected, the presence of the cyano group directs the rearrangement wherein the aryl group adjacent to the cyano becomes part of the naphthol. Upon workup of the Lewis acid-mediated reaction, the cyanohydrin collapses to reveal the enol **16**, and the crude mixture was then triflated to converge the isomeric mixture to a single product.[12] Triflated product **17** underwent further elaboration, with a specific focus on lignan analog synthesis to **18-22** as multi-functionalized dihydronaphthalenes *via* Pd-catalyzed hydrogenations and Suzuki-Miyaura couplings in good yields over 4 steps.[13] Notably, dihydronaphthalenes **20** and **21** were previously unattainable as a single product *via* our previous method.[4] Thus, the newly integrated cyano group now provides straightforward access to lignan derivatives as a single regioisomer.

Lastly, we targeted two natural products that are aryl group regioisomers, isodiphyllin (**24**) and diphyllin (**25**), both of which possess potent antiviral activities.[14] Deprotection of the triflated dihydronaphthalene **17** by tetrabutylammonium hydroxide afforded the saturated hydroxy arylnaphthalene **23**, a key scaffold intermediate that can be readily mapped to several known natural products.[15] Subsequent regioselective reduction and lactonization of the most accessible ester using borane dimethyl sulfide yielded **24** and **25** respectively (49, 53%).[16] To the best of our knowledge, this is the first example of the rearrangement of cyano-tetrahydrofurans to selective dihydronaphthol derivatives.

Scheme 4. Synthesis of Diphyllin, Isodiphyllin, and dihydronaphthalenes from α-cyano epoxides and dimethyl fumarate



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In summary, we have advanced photoredox methodologies through the strategic utilization of α-cyano epoxides and an exploration of their reactivity in [3+2] cycloaddition *via* organo-photoredox. The investigations reveal that temperature variations and anionic charge localization influence the regioselectivity of photoredox generated carbonyl ylides. Leveraging α-cyano epoxides has enabled us to access complex lignan natural products isodiphyllin and diphyllin as single products, along with the synthesis of functionalized furans. The development of these scaffolds stands as a crucial step towards expanding the repertoire of synthetic analogs, holding great promise for drug discovery and therapeutic interventions.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

General information, experimental procedures, and characterization data for all new compounds (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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